

### **REMARKS**

Applicant respectfully requests entry of amendments to claims 1-5, 16, 22, and 32-35, and canceling claim 18. Claims 19-21 are withdrawn without prejudice or disclaimer. Support for the amendments can be found throughout the specification, including paragraphs [0024]-[0027], and [0102], Figure 4, and the originally filed claims and, therefore, do not add new matter.

Applicant submits that pending claims 1-17 and 22-36 are in condition for allowance, and respectfully requests that the claims as amended be entered.

### **Objections**

Applicant has provided herewith an amendment to the Abstract, where the language objected to has been removed.

Applicant has provided herewith an amendment to the Specification, where the missing patent serial number has been inserted.

Applicant has provided herewith an amendment to claim 5 which corrects the missing punctuation mark identified in the Action.

For these reasons, Applicant respectfully requests that the objections be withdrawn.

### **Restriction Requirement**

Applicant affirms the election of Group I, drawn to claims 1-18 and 22-32 and acknowledges that Groups I and III, drawn to claims 1-18 and 22-36, have been rejoined.

### **Rejections Under 35 U.S.C. §102**

Claims 1, 5-7, 9, 10, and 13-18 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Cao et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below. As claim 18 has been canceled, the rejection as applied to this claim is rendered moot.

The Office Action alleges, in pertinent part, that the cited reference teaches the elements as recited in the present claims. However, Cao et al. do not teach the use of a primary amine as an enhancer for detecting a Raman signal generated by an irradiated nucleic acid.

Cao et al. expressly recite the use of an Ag enhancement solution (Ted Pella, Inc., Redding, California). Applicant submits that the Ag enhancement solution does not use a primary amine for enhancing the Raman signal (see Exhibit A, Ted Pella, Inc., "Silver Enhancement Kits, Protein and Nucleic Acid Stains").

The present claims expressly recite "a primary amine having an alkyl chain of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 25 carbon atoms".

As stated in *Hybritech Inc. v. Monoclonal Antibody, Inc.*, 231 USPQ 81 (Fed. Cir. 1986),  
"It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention."

Therefore, because the instant claims recite "primary amines having an alkyl chain of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 25 carbon atoms" for enhancement, the Cao et al. reference does not anticipate the claimed invention.

Failure of the prior art to meet every element of the claimed invention does not meet the standard under 102. For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Claims 22-25 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Bruchez, Jr. et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the cited reference teaches the elements as recited in the present claims. However, Bruchez, Jr. et al. do not apply an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra as presently claimed.

As stated in *Hybritech Inc. v. Monoclonal Antibody, Inc.*, 231 USPQ 81 (Fed. Cir. 1986),  
“It is axiomatic that for prior art to anticipate under 102 it has to meet every  
element of the claimed invention.”

Therefore, because the instant claims recite “applying an alternating current (AC) to the  
probe-target complex prior to detection, wherein the applied AC enhances the difference in the  
affect of the first probe on the second probe fluorescent signal or Raman spectra,” the Bruchez,  
Jr. et al. reference does not anticipate the claimed invention.

Failure of the prior art to meet every element of the claimed invention does not meet the  
standard under 102. For these reasons, Applicant respectfully requests that the rejection be  
withdrawn.

Claims 33-36 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by  
Vo-Dinh.

Applicant traverses the rejection as it might apply to the amended claims, including  
claims dependent therefrom, for the reasons given below.

Notwithstanding the amendments to the claims, Applicant submits that the following  
statement in the Office Action is incorrect:

“With regard to Claim 36, the instant specification does not limit the nucleic acid  
to only pyrimidine residues.”

Whether the specification does or does not limit the claim is immaterial if the claim does  
so limit. It is well settled case law that in looking into the specification to construe claim terms,  
care must be taken to avoid reading a limitation appearing in the specification into the claims.  
See, e.g., SRI International v. Matsushita Elec. Corp., 227 U.S.P.Q. 577 (Fed. Cir. 1985) (*en  
banc*). Applicant submits that such care was not taken in this case.

Nevertheless, the Office Action alleges, in pertinent part, that the cited reference teaches  
the elements as recited in the present claims. Applicant submits that, while Vo-Dinh may or  
may not teach aminoacridine as an SER label, aminoacridine is not a primary amine having an  
alkyl chain of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 25 carbon atoms.

As stated in *Hybritech Inc. v. Monoclonal Antibody, Inc.*, 231 USPQ 81 (Fed. Cir. 1986),  
“It is axiomatic that for prior art to anticipate under 102 it has to meet every  
element of the claimed invention.”

Therefore, because the instant claims recite “a primary amine having an alkyl chain of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 25 carbon atoms,” the Vo-Dinh reference does not anticipate the claimed invention.

Failure of the prior art to meet every element of the claimed invention does not meet the standard under 102. For these reasons, Applicant respectfully requests that the rejection be withdrawn.

#### **Rejections Under 35 U.S.C. §103**

Claims 2-4 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Cao et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First there must be some suggestion or motivation in the references themselves or in knowledge generally available to one of skill in the art, to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. And, finally the prior art reference (or references when combined) must teach all claim limitations. The teaching or suggestion and reasonable expectation of success must both be found in the prior art and not in Applicant's disclosure. (See MPEP §706.02(j)).

Applicant submits that because the cited reference does not suggest modifying the reference teachings, the reference does not teach all of the elements of the invention as claimed.

The Office Action alleges, in pertinent part, that Cao et al. is silent with respect to teaching other Raman probes which could be used in the method of SNP sequencing. The Action goes on to state that the reference teaches “another method of determining if multiple dyes could be used in a multiplex method,” and that “Cao et al. teaches [sic] one of the Raman probes that can be used is rhodamine (e.g., an amine).” Notwithstanding the amendments to the

claims, while Cao et al. may or may not teach rhodamine as a useful dye in a multiplex method, rhodamine is not a primary amine. Further, Cao et al. do not teach rhodamine as a component of the enhancement solution used for Raman scattering. As stated above, Cao et al. expressly teach an enhancement solution that does not use primary amines, moreover, the reference teaches the use of rhodamine as an SER label, not as an enhancer.

The present specification teaches that, in the **absence of other labels**, Raman signaling can be enhanced by the use of a primary amine (see, e.g., paragraphs [0024]-[0027] and Figure 4 of the instant specification). Applicant submits that one of skill in the art would not know to substitute a primary amine for the enhancement solution as taught by Cao et al., in the absence of Applicant's teachings.

As stated above, the teaching or suggestion must be found in the cited art. One cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Because there is no suggestion for substituting the enhancement solution of Cao et al. for a primary amine, no *prima facie* case of obviousness has been established.

Applicant submits that because there is no suggestion in the cited art to modify the reference, Cao et al. do not teach all of the elements as claimed, thus, no *prima facie* case for obviousness exists. For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claim 12 stands rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Cao et al. in view of Lane et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicant submits that because the cited references do not suggest modifying the primary reference teachings, the references do not teach all of the elements of the invention as claimed.

The Office Action alleges, in pertinent part, that the primary reference is silent with respect to teaching a method in which the capture probe and oligonucleotide probe are ligated. The Action then provides Lane et al. to cure the deficiency identified in the primary reference. However, review of Lane et al. demonstrates that the reference does not teach the substitution of

a primary amine for the enhancement solution as taught by Cao et al., an element presently recited in the claim from which claim 12 is dependent.

Because the teachings of Lane et al. would not result in a method using a primary amine enhancer as claimed when combined with the teachings of Cao et al., in the absence of Applicant's specification all of the claim elements would not be taught. Therefore, one of skill in the art would not be motivated to combine such teachings.

As stated above, the teaching or suggestion must be found in the cited art. One cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Because there is no suggestion for substituting the enhancement solution of Cao et al. for a primary amine, which is not cured by the teachings of Lane et al., no *prima facie* case of obviousness has been established.

Applicant submits that because there is no teaching of the elements as claimed, there is no motivation to combine the cited references, thus, no *prima facie* case for obviousness exists. For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claims 1, 5-11 and 14-18 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Pastinen et al. in view of Cao et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below. As claim 18 has been canceled, the rejection as applied to this claim is rendered moot.

Applicant submits that because the cited references do not suggest modifying the primary reference teachings, the references do not teach all of the elements of the invention as claimed.

Notwithstanding the amendments to the claims, Applicant submits that based on the statement "If you are targeting occurrences of a nucleotide it is inherent that the targeting would be the detection of nucleotide occurrences of a target segment," the Office Action misapprehends technology that uses allele specific primers. Allele specific primers are directed to single nucleotides in an allele as they are complementary to the single nucleotide (see legend to Figure 1, page 1033 of the cited reference), thus if more than one adjacent nucleotide is to be detected,

allele specific primers are not designed to detect such occurrences. Claim 8 specifically recites a series of nucleotide occurrences at adjacent positions (disclosed at paragraph [0049]), which requires the method to be able to detect one occurrence and more than one occurrence conjunctively, not disjunctively (i.e., as an alternative). As such, extension by a single nucleotide as recited in Pastinen et al. would not be inherently teaching detection as presently claimed because the cited reference can only detect one occurrence, not a series of occurrences.

Nevertheless, the Office Action alleges, in pertinent part, that the primary reference is silent with respect to teaching a method in which Raman probes are used instead of labeled dNTPs to determine sequence identity. The Action then provides Cao et al. to cure the deficiency identified in the primary reference. However, Cao et al. does not teach or suggest replacement of the allele specific primer/extension step of Pastinen et al. by using oligonucleotide binding (which oligonucleotide is defined as comprising at least 2 nucleotides, at paragraph [0057] of the instant application) and an enhancer to determine nucleotide identity nor does Pastinen et al. teach the substitution of a primary amine for the enhancement solution as taught by Cao et al. to determine nucleotide identity.

Because the teachings of Cao et al. would not teach the elements as claimed when combined with the teachings of Pastinen et al., one of skill in the art would not be motivated to combine such teachings.

As stated above, the teaching or suggestion must be found in the cited art. One cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Because there is no suggestion for substituting the allele specific primer/extension step of Pastiene et al. for oligonucleotide binding to detect nucleotide identity or the substitution of the enhancement solution of Cao et al. for a primary amine to detect nucleotide identity, no *prima facie* case of obviousness has been established.

Applicant submits that because there is no teaching of the elements as claimed, there is no motivation to combine the cited references, thus, no *prima facie* case for obviousness exists. For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claims 22-27 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Cao et al. in view of Bruchez, Jr. et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicant submits that because the cited references do not suggest modifying the primary reference teachings, the references do not teach all of the elements of the invention as claimed.

The Office Action alleges, in pertinent part, that the primary reference is silent with respect to teaching a method in which probes have a first and second signal attached. The Action then provides Bruchez, Jr. et al. to cure the deficiency identified in the primary reference. However, review of Bruchez, Jr. et al. demonstrates that the reference does not teach the application of an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra, an element presently recited in the claims.

Because the teachings of Bruchez, Jr. et al. would not result in a method of applying an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra as claimed when combined with the teachings of Cao et al., all of the claim elements would not be taught. Therefore, one of skill in the art would not be motivated to combine such teachings.

As stated above, the teaching or suggestion must be found in the cited art. One cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Because there is no suggestion for applying an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra in the primary reference, which is not cured by the teachings of Bruchez, Jr. et al., no *prima facie* case of obviousness has been established.

Applicant submits that because there is no teaching of the elements as claimed, there is no motivation to combine the cited references, thus, no *prima facie* case for obviousness exists.



For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claim 28 stands rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Bruchez, Jr. et al. in view of Livak et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicant submits that because the cited references do not suggest modifying the primary reference teachings, the references do not teach all of the elements of the invention as claimed.

The Office Action alleges, in pertinent part, that the primary reference is silent with respect to teaching the distance the quencher and reporter should be separated. The Action then provides Livak et al. to cure the deficiency identified in the primary reference. However, review of Livak et al. demonstrates that the reference does not teach applying an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra, an element presently recited in the claim.

Because the teachings of Livak et al. would not result in a method where application of an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra using a primary amine enhancer as claimed when combined with the teachings of Bruchez, Jr. et al., all of the claim elements would not be taught. Therefore, one of skill in the art would not be motivated to combine such teachings.

As stated above, the teaching or suggestion must be found in the cited art. One cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Because there is no suggestion for applying an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra in the primary reference, which is not cured by the teachings of Livak et al., no *prima facie* case of obviousness has been established.

Applicant submits that because there is no teaching of the elements as claimed, there is no motivation to combine the cited references, thus, no *prima facie* case for obviousness exists. For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claims 30-32 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Brunchez, Jr. et al. in view of Chan et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicant submits that because the cited references do not suggest modifying the primary reference teachings, the references do not teach all of the elements of the invention as claimed.

The Office Action alleges, in pertinent part, that the primary reference is silent with respect to teaching a method in which each nucleotide is read as it passes through a channel have a first and second signal attached. The Action then provides Chan et al. to cure the deficiency identified in the primary reference. However, Bruchez, Jr. et al. do not teach the application of an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra an element presently recited in the claim. And while Chan et al. may or may not teach using current to move molecules across a detection component, the reference does not teach the application of current prior to detection to enhance the difference in the affect of a first probe on a second probe as presently claimed.

Because the teachings of Bruchez, Jr. et al. would not result in a method of applying an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra as claimed when combined with the teachings of Chan et al., all of the claim elements would not be taught. Therefore, one of skill in the art would not be motivated to combine such teachings.

As stated above, the teaching or suggestion must be found in the cited art. One cannot simple use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed.

Cir. 1985). Because there is no suggestion for applying an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra in the primary reference, which is not cured by the teachings of Chan et al., no *prima facie* case of obviousness has been established.

Applicant submits that because there is no teaching of the elements as claimed, there is no motivation to combine the cited references, thus, no *prima facie* case for obviousness exists. For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

In re Application of:  
Xing Su  
Application No.: 10/748,374  
Filing Date: December 29, 2003  
Page 21

PATENT  
Attorney Docket No. INTEL1150(P15618)


**Conclusion**

Applicant submits that pending claims 1-17 and 22-36 are in condition for allowance. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this submission.

No fee is deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees required by this submission, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number. A duplicate copy the Transmittal Sheet is enclosed.

Respectfully submitted,

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